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Single-neuron activity in the nucleus accumbens on the extinction and reinstatement Morphine-induced conditioned place preference: The key role of the NMDA and AMPA receptors in the reward-associated behaviors

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Background & Aim: The mesocorticolimbic dopaminergic system projecting from the Ventral Tegmental Area (VTA) to the Nucleus Accumbens (NAc) is necessary for the initiation of opioid compulsive usage and reward-associated behaviors. Activation of AMPA and NMDA glutamatergic receptors in the nucleus accumbens probably is a part of the mechanism of drug related reward. In this work, we investigated on the effects intracerebro-ventricular administration the AMPA (CNQX) and NMDA (AP5) antagonist on both extinction and reinstatement of morphine-induced Conditioned Place Preference (CPP).

Materials & Methods: All animals passed CPP procedure and afterwards, received intracerebro-ventricular administration of different doses of D-AP5 or CNQX during extinction period or reinstatement phase. The conditioning scores were recorded by Ethovision software. After behavioral test in the reinstatement day, the prefrontal cortex, nucleus accumbens and hippocampus were then removed and the levels of c-fos, CREB, and phosphorylated-CREB were measured using western blotting. *In vivo* single unit recording after the extinction period were performed in urethane anesthetized rats. After 20 min of baseline recording from accumbens neurons the non-effective dose of morphine (1 mg/kg; S.C.) were performed and the spontaneous firing were continued to be recorded for 40 min.

Results: Our results showed that administration of D-AP5 or CNQX significantly shortened the extinction (maintenance) of morphine CPP. Besides, injection of these antagonists before administration of priming dose of morphine (1 mg/kg, subcutaneously) following extinction period decreased the reinstatement of morphine CPP in extinguished rats. However, the effect of CNQX on maintenance and reinstatement of morphine was more significant than D-AP5. In the molecular session ICV microinjection mentioned antagonists decreased c-Fos level and CREB/pCREB rate and also, the electrophysiology session ICV microinjection these antagonists increased baseline firing of the nucleus accumbens neurons.

Conclusion: These findings suggested that glutamate receptors involve in extinction and reinstatement of morphine-CPP and antagonism of these receptors may be useful for faster extinction of drug-induced reward and attenuation of relapse.

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